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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANDERSON, JAMES D	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/706,328	HANNAH ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38,49-51,53-58,67 and 69-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-38,49-51,53-58,67 and 69-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/16/2009 and 4/22/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 1/15/2009, are acknowledged and entered. Claim 68 has been cancelled by Applicant. Claims 1-38, 49-51, 53-58, 67, and 69-71 are pending and under examination.

Response to Arguments

Any previous rejections and/or objections to claim 68 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

In light of the new rejections set forth in the present Office Action not necessitated by Applicant's amendments to the claims, this Office Action is non-final.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 1/16/2009. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

Priority

As discussed in the Office Action mailed 11/2/2006, the disclosures of the prior-filed Application Nos. 60/426,107; 60/426,282; 60/426,226; 60/426,204; 60/460,328; 60/460,493; 60/460,327; 60/460,369; and 60/478,916, fail to provide adequate written support or enablement in the manner provided by the first paragraph of 35 U.S.C. § 112 for one or more claims of this application. The cited U.S. Provisional Applications fail to provide adequate support for the instantly claimed limitations of C_{max}, ng/ml blood or plasma levels, AUC, and dose ranges.

Support for the instantly claimed invention was found in U.S. Provisional Application No. 60/517,915, filed 11/7/2003 (see especially Claims).

As such, the earliest effective U.S. filing date of the instantly claimed invention has been determined to be **November 7, 2003**.

Specification

The use of the trademark Tetrarome® has been noted in this application (*e.g.*, page 6, [0014]). It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-38, 49-51, 53-58, 67, and 69-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There are numerous abbreviations recited in the claims (*e.g.*, "PDGFR", "FLT-3", "C_{max}", "AUC"). The first use of an abbreviation in the claims should be preceded by the full meaning of the abbreviated term so as to clearly and unequivocally convey what the abbreviation is intended to mean. It is noted that some abbreviations used in the claims are defined in the specification. However, Applicants are reminded that limitations in the specification are not imported into the claims.

Claims 18-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 18 appears to contain the trade name Tetrarome®. M.P.E.P. § 2173.05(u)

states, "It is important to recognize that a trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus a trademark or trade name does not identify or describe the goods associated with the trademark or trade name." If the trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. § 112, second paragraph. *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982).

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-29, 31-38, 49-51, and 53-58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to methods of treating cancer, wherein the cancer comprises cells expressing a receptor tyrosine kinase selected from the group consisting of PDGFR, c-Kit, and FLT-3.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to the treatment of cancers that were not adequately described in the specification.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(i), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

Nowhere in the instant specification do Applicants provide any description of what cancers express PDGFR, c-Kit, or FLT-3 *versus* those cancers that do not express these receptor tyrosine kinases. Neither do Applicants disclose a method of assessing whether a cancer comprises cells expressing PDGFR, c-Kit, or FLT-3. Applicants disclose that the claimed compounds can be used to treat cancer, including leukemias and solid tumors (page 4, [0011]). Specific cancers to be treated using the claimed methods are described at page 7, [0018]. However, nowhere do Applicants distinguish between cancers that express the particular receptor tyrosine kinases recited in the instant claims or provide any means to determine whether a cancer comprises cells expressing PDGFR, c-Kit, or FLT-3.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a generic genus of cancers purported to express PDGFR, c-Kit, or FLT-3. One of skill in the art would not

recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claims 1-38, 49-51, 53-58, 67, and 69-71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "treating" cancer to the extent that treating refers to alleviating the symptoms associated with cancer or halting the further progression or worsening of symptoms of cancer, does not reasonably provide enablement for "treating" cancer to the extent that treating refers to prevention or prophylaxis of cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to "treating" cancer comprising administering a compound of the formula recited in claim 1. Applicants define "treating" at page 16, [0041] of the instant specification. In this regard, Applicants state that "treating" within the context of the instant invention means an alleviation of symptoms associated with a disorder or disease, or halt of further progression or worsening of those symptoms, or **prevention or prophylaxis of the disease or disorder**. For example, within the context of cancer, successful treatment may include an alleviation of symptoms or halting the progression of the disease, as measured by a reduction in the growth rate of a tumor, a halt in the growth of the tumor, a reduction in the size of a tumor, **partial or complete remission of the cancer**, or increased survival rate or clinical benefit. Thus, pursuant to Applicant's definition of "treating", the instant claims encompass an embodiment wherein the claimed compound is used to prevent or cure cancer.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

The state of the art with respect to cancer chemotherapy is that while reduction of tumor growth with chemotherapeutic agents is recognized as being effective therapy, the prevention or curing of cancer is something which is presently not recognized as being possible. While there are some small organic molecules that have been shown to reduce the incidence of cancer in animal tumor models, there use in the clinic has been limited. As such, while one skilled in the art would reasonably expect the claimed compound to have efficacy in reducing tumor growth in vivo, the skilled artisan would not expect that the claimed compound would be useful in preventing or curing cancer as broadly encompassed by Applicant's definition of "treating".

2. The breadth of the claims

The claims are extremely broad insofar as they disclose the general "treatment" of cancer wherein the cancer comprises cells expressing a receptor tyrosine kinase selected from the group consisting of PDGFR, c-Kit, and FLT-3 with the same compound. Applicant's definition of

"treating" as set forth in the instant specification encompasses the prevention and cure of such cancers.

3. The amount of direction or guidance provided and the presence or absence of working examples

Applicant's working examples with respect to "treating" cancer are limited to in vitro assays demonstrating that the claimed compound has EC50 values ranging from 1 to 10 μM in various cancer cells lines in vitro (Example 1; Table 1); that the claimed compound inhibits various receptor tyrosine kinases in vitro (Example 3; Table 3); that the claimed compound inhibits colon tumor growth in vivo (Example 4; Table 4); and that the claimed compound inhibits prostate tumor growth in vivo (Example 5; Table 7). Nowhere do Applicants provide any demonstration that the claimed compound prevents or cures any cancer expressing PDGFR, c-Kit, or FLT-3.

Applicants provide guidance with respect to treating cancer in the form of doses, C_{max} values, plasma concentrations, and dosing regimens expected to result in therapeutic efficacy (see claims). However, other than the colon and prostate tumor models, Applicants have not tested the claimed compound for reduction of tumor growth in any other cancer types.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed compound could be predictably used to prevent or cure cancers expressing PDGFR, c-Kit, or FLT-3 as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because the instantly claimed compound inhibits PDGFR, c-Kit, and FLT-3 kinases it must therefore, *a priori*, be

useful in the treatment of cancers expressing these tyrosine kinases cell. However, Applicant's definition of "treating" as used in the instant claims encompasses both the prevention and curing of cancer. Nowhere have Applicants demonstrated that such prevention or curing is possible using the claimed compound.

Applicants tested the claimed compound for inhibition of tyrosine kinases. The claimed compound was found to inhibit PDGFR, c-Kit, and FLT-3 with IC_{50}s of 0.027 μM, 0.0001 μM, and 0.0015 μM, respectively (Table 3). Subsequently, Applicants demonstrate that the claimed compound inhibits prostate and colon tumor growth *in vivo*, however there is no indication in the specification that these tumors comprised cells expressing PDGFR, c-Kit, or FLT-3.

Determining if any particular claimed compound would prevent or cure any particular cancerous disease state would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants with respect to the prevention or curing of cancer as broadly encompassed by the claimed "treating".

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 9-13, 17, 19-30, 35-38, 49, 53-58, 67, and 69-71 are rejected under 35 U.S.C. 103(a) as being obvious over **Renhowe *et al.*** (USP No. 6,605,617 B2; Issued Aug. 12, 2003; Filed Sep. 11, 2001) and **Foekens *et al.*** (Cancer Research, 2001, vol. 61, pages 5407-5414) (newly cited) in view of **"Guideline for the Format and Content of the Human Pharmacokinetic and Bioavailability Section of an Application"** (Center for Drugs and Biologics, FDA, Department of Health and Human Services, February 1997, pages 1-18).

The applied reference (Renhowe *et al.*) has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The instant claims recite methods of treating cancers comprising cells expressing a receptor tyrosine kinase selected from the group consisting of PDGFR, c-Kit, and FLT-3, comprising administering 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one in amounts to provide ranges of C_{max}, ng/mL, and AUC values as recited in the instant claims.

Renhowe *et al.* teach a genus of compounds that are small molecule inhibitors of vascular endothelial growth factor (VEGF) receptor tyrosine kinases for treating diseases characterized by angiogenesis, including cancer (col. 1, lines 11-21). Members of the VEGF subfamily of

receptor tyrosine kinases are taught to induce vascular permeability and endothelial cell proliferation and to induce angiogenesis and vasculogenesis (col. 2, lines 13-16).

Accordingly, the inventors sought to develop compounds that inhibit the proliferation of capillaries, inhibit the growth of tumors, and/or inhibit vascular endothelial growth factor receptor tyrosine kinase (col. 3, lines 27-35). To this end, the inventors teach a genus of quinolinone compounds (col. 3, line 39 to col. 18, line 21), of which the instantly claimed compound is a specie and is explicitly recited as Example 109 at column 86, lines 64-66 and column 97, lines 23-24. This compound, along with a series of other compounds, is to have an IC_{50} value of less than 10 μM with respect to VEGFR1, VEGFR2, and bFGF (col. 101, lines 45-47).

With regard to claims 17 and 19-22, the compounds disclosed in Renhowe *et al.* may be formulated in pharmaceutical compositions comprising pharmaceutically acceptable carriers, excipients, binders, diluents, and the like (col. 57, lines 62-66) as well as thickeners, buffers, sweeteners, and flavoring agents (col. 59, line 1). Liquid dosage forms comprising water as recited in claim 19 are disclosed at column 59, lines 5-14, lines 37-47, and lines 48-59.

With regard to claim 23, the compounds of the invention may be formulated in compositions for various routes of administration (col. 57, line 62 to col. 60, lines 32), such as in injectable dosage forms (col. 59, lines 37-59).

With regard to claims 24 and 35, specific dosages of the compounds of the invention may be adjusted depending on conditions of the disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs (col. 60, lines 33-37). Any of the dosage forms containing effective amounts are taught to be "well within the bounds of routine experimentation and therefore, well within the scope of the instant invention" (col. 60, lines 38-40). As such, administration of the compounds of Renhowe et al. necessarily include at least administration once a day as recited to claims 24 and 35.

With regard to claims 25-27, which recite doses of 0.25 to 30 mg/kg body weight (claim 25), 25 to 1500 mg/day (claim 26), and 200 to 500 mg/day (claim 27), Renhowe *et al.* do not explicitly disclose the amounts of the disclosed compounds. However, Renhowe *et al.* do teach that the compounds of their invention are administered in an "effective amount" and that specific

dosages of the compounds of the invention may be adjusted depending on conditions of the disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs (col. 60, lines 33-37). As such, the claimed doses are not seen as being a patentable distinction over Renhowe *et al.* who teach, suggest, and motivate the administration of compounds of their invention in an effective amount to treat the disclosed conditions. One skilled in the art at the time the invention was made would have been motivated to determine optimal doses of the claimed compound for administration to a subject having cancer as suggested and motivated by the teachings of Renhowe *et al.*

With regard to "treating", the inventors teach that this means, for example, within the context of treating patients in need of an inhibitor of VEGF-RTK, a reduction in the proliferation of capillaries feeding a tumor or diseased tissue, an alleviation of symptoms related to a cancerous growth or tumor, proliferation of capillaries, or diseased tissue, a halting in capillary proliferation, or a halting in the progression of a disease such as cancer or in the growth of cancerous cells (col. 60, lines 52-63).

With regard to claims 57 and 58, which recite metabolites of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one, the administration of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one to a patient as suggested and motivated by Renhowe *et al.* will necessarily result in the "administration" of the metabolites of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one as recited in the instant claims because such metabolites are formed, by definition, by the action of enzymes in the body of a patient administered 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one.

With regard to claims 67 and 69-71, Renhowe *et al.* disclose methods of inhibiting the proliferation of capillaries, inhibiting the growth of tumors, and/or inhibiting vascular endothelial growth factor receptor tyrosine kinase comprising administering inhibitors of VEGF. They do not explicitly teach the treatment of the cancers recited in claims 67 and 69-71. However, Foekens *et al.* teach that increased expression level of VEGF mRNA or protein is associated with poor prognosis in primary **breast cancer** patients (page 5407, right column). As such, it would have been obvious to administer the VEGF inhibitors disclosed in Renhowe *et al.* to treat breast

cancer because breast cancer is clearly a cancer expressing VEGF. As claims 67 and 69-71 depend from claims 1, 36, 49, and 53, respectively, which recite administering the claimed compound to treat a cancer expressing PDGFR, c-Kit, or FLT-3, breast cancer is clearly also a cancer expressing PDGFR, c-Kit, or FLT-3 as recited in instant claims 1-6, 9-13, 17, 19-24, 28-30, 35-38, 49, 53-58, 67, and 69-71.

While Renhowe *et al.* do not disclose that administration of the compounds of their invention, including the claimed compound, provide the C_{max}, ng/mL in plasma or blood, or AUC values recited in the instant claims, in the absence of evidence to the contrary administration of an "effective amount" of the compounds of Renhowe *et al.* to treat breast cancer will necessarily result in the claimed C_{max}, ng/mL in plasma or blood, and AUC values recited in the instant claims. Applicant's characterization of the pharmacokinetics of administration of the claimed compound is not seen as a patentable distinction over the administration of an "effective amount" as disclosed in Renhowe *et al.* Further, the FDA guidelines for the format and content of the human pharmacokinetic and bioavailability section of a New Drug Application teaches that biopharmaceutic studies are required by the Food, Drug, and Cosmetic Act (page 1). Such studies include pharmacokinetic studies assessing the time course of drug and major metabolite concentrations in blood and other body compartments (pages 3-4). The studies provided in support of a New Drug Application, the most critical information is that showing (by measurement of plasma drug levels) the rate of drug absorption and delivery to the systemic circulation, and the rate of elimination by metabolic or excretory processes (page 4). Pharmacokinetic parameters should include C_{max}, AUC, t_{max}, K_{el}, V_d, etc. derived from each *in vivo* study (page 6).

Accordingly, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer a therapeutically effective amount of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one to a patient in need thereof (*e.g.*, a patient having a cancer or tumor with cells expressing VEGFR1, VEGFR2, and/or bFGF, such as breast cancer). In support of the obviousness of the claimed methods, the Examiner makes the following findings of fact:

(i) The instantly claimed compound and related compounds were known in the art and were known to inhibit at least VEGFR1, VEGFR2, and bFGF;

(ii) Inhibition of such receptor tyrosine kinases was suggested by the prior art to be useful in the treatment of cancers;

(iii) Therapeutically effective amounts of the claimed compound are suggested by the prior art to vary depending on the route of administration and dosage form;

(iv) Breast cancer was known to express VEGF; and

(v) Measuring pharmacokinetic parameters such as C_{max}, AUC, t_{max}, K_{el}, V_d, etc. derived from *in vivo* studies is a requirement before a new drug can be approved for use in human patients.

Thus, Renhowe *et al.* provide explicit teaching, suggestion, and motivation to administer the instantly claimed compound and structurally related compounds to patients in need thereof, which patients include those having a cancer or tumor with expressing a vascular endothelial growth factor receptor tyrosine kinase, such as breast cancer as recited in the instant claims. As evidenced by Applicant's dependent claims 67 and 69-71, breast cancer is a cancer expressing PDGFR, c-Kit, or FLT-3 as recited in the independent claims.

The skilled artisan would have been motivated to administer the claimed compound to treat a cancer expressing VEGF as suggested by the teachings of Renhowe *et al.* In view of the teachings of Foekens *et al.*, the skilled artisan would have been imbued with at least a reasonable expectation that administration of a compound disclosed in Renhowe *et al.* would be effective to treat breast cancer because breast cancer was known to express VEGF which was known to be associated with poor prognosis in primary breast cancer patients. With respect to the claimed pharmacokinetic values, Applicants have presented no evidence that administration of an effective amount of a compound disclosed in Renhowe et al., including the instantly claimed compound, to treat breast cancer in a patient will not result in the Cmax, ng/mL in blood or plasma, or AUC ranges recited in the instant claims. As such, in the absence of such evidence, it is the position of the Examiner that administration of the claimed compound to treat breast cancer in a subject as suggested and motivated by the teachings of Renhowe *et al.* and Foekens *et al.* necessarily meets these claim limitations.

Claims 7-8 and 14-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Renhowe *et al.*** (USP No. 6,605,617 B2; Issued Aug. 12, 2003; Filed Sep. 11, 2001) and

Foekens *et al.* (Cancer Research, 2001, vol. 61, pages 5407-5414) (newly cited) in view of **"Guideline for the Format and Content of the Human Pharmacokinetic and Bioavailability Section of an Application"** (Center for Drugs and Biologics, FDA, Department of Health and Human Services, February 1997, pages 1-18), as applied to claims 1-6, 9-13, 17, 19-30, 35-38, 49, 53-58, 67, and 69-71 above, and further in view of **Berge *et al.*** (J. Pharm. Sci., 1977, vol. 66, no. 1, pages 1-19).

Renhowe *et al.*, Foekens *et al.*, and the FDA Guidelines teach as discussed *supra* and are applied herein in their entirety for the same teachings. Claims 7-8, 14 and 15 differ from Renhowe *et al.* and the FDA Guidelines in the recitation of administration of the lactate salt of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one.

However, Berge *et al.* teach that the chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form (page 1, left column). In this regard, Berge *et al.* teach a list of FDA approved commercially marketed salts, including the instantly claimed lactate salt (Table 1).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one as taught in Renhowe *et al.* as a lactate salt. It is noted that Renhowe *et al.* teach that pharmaceutically acceptable salts and tautomers of the disclosed compounds are encompassed by their invention (col. 57, lines 64-65). The skilled artisan would have been motivated to do so because Renhowe *et al.* teach that pharmaceutically acceptable salts of the compounds of their invention may be used in compositions for treating patients and Berge *et al.* teach that lactate salts of pharmaceutical agents are suitable salts approved by the FDA. As such, the skilled artisan would have been imbued with at least a reasonable expectation that a lactate salt of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one could be formed and would be useful in the methods taught, suggested, and motivated by Renhowe *et al.* (*i.e.*, treatment of patients).

Claims 16 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Renhowe *et al.*** (USP No. 6,605,617 B2; Issued Aug. 12, 2003; Filed Sep. 11, 2001) and **Foekens *et al.*** (Cancer Research, 2001, vol. 61, pages 5407-5414) (newly cited) in view of

"Guideline for the Format and Content of the Human Pharmacokinetic and Bioavailability Section of an Application" (Center for Drugs and Biologics, FDA, Department of Health and Human Services, February 1997, pages 1-18), as applied to claims 1-6, 9-13, 17, 19-30, 35-38, 49, 53-58, 67, and 69-71 above, and further in view of **Lindell *et al.*** (US 2003/0159702 A1; Published Aug. 28, 2003; Filed Jan. 16, 2003).

Renhowe *et al.*, Foekens *et al.*, and the FDA Guidelines teach as discussed *supra* and are applied herein in their entirety for the same teachings. Claims 16 and 18 differ from Renhowe *et al.*, Foekens *et al.*, and the FDA Guidelines in the recitation of the specific sweetener, fructose, and the specific flavoring agent, mandarine.

However, Lindell *et al.* disclose that fructose is a known sweetening agent useful in pharmaceutical compositions (page 5, [0094] to page 6, [0099]) and that mandarine is a known flavoring agent (page 6, [0100]).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used and known sweetener and flavoring agent in the formulation of a pharmaceutical composition for the administration of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one. Renhowe *et al.* generally disclose that pharmaceutical compositions comprising compounds of their invention can be formulated with sweeteners and flavoring agents. As such, there is nothing unobvious or inventive about using known sweeteners and flavoring agents, such as those disclosed in Lindell *et al.*, in the formulation of a pharmaceutical composition of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one for administration to a patient.

Claims 31-34 and 50-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Renhowe *et al.*** (USP No. 6,605,617 B2; Issued Aug. 12, 2003; Filed Sep. 11, 2001) and **Foekens *et al.*** (Cancer Research, 2001, vol. 61, pages 5407-5414) (newly cited) in view of **"Guideline for the Format and Content of the Human Pharmacokinetic and Bioavailability Section of an Application"** (Center for Drugs and Biologics, FDA, Department of Health and Human Services, February 1997, pages 1-18), as applied to claims 1-6, 9-13, 17, 19-30, 35-38, 49, 53-58, 67, and 69-71 above, and further in view of **Cecil Textbook of Medicine** (21st Edition, vol. 1, 2000, eds. Goldman and Bennett, pages 1060-1074).

Renhowe *et al.*, Foekens *et al.*, and the FDA Guidelines teach as discussed *supra* and are applied herein in their entirety for the same teachings. Claims 31-34 and 50-51 differ from Renhowe *et al.*, Foekens *et al.*, and the FDA Guidelines in the recitation of specific dosing regimens for administration of the claimed compound. While Renhowe *et al.* suggest that specific dosages of the compounds of the invention may be adjusted depending on conditions of the disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs (col. 60, lines 33-37), the reference does not explicitly suggest the claimed treatment cycles or dosing intervals recited in claims 31-34 and 50-51.

The Cecil Textbook of Medicine discusses principles of cancer therapy, including development of a treatment plan, pharmacokinetic considerations, and dosing regimens for antineoplastic agents. With regard to pharmacokinetic considerations, the authors state that the intravenous route of a drug is preferable for most cytotoxic anticancer drugs because it ensures adequate plasma levels while minimizing compliance problems (page 1064, right column). For some agents, continuous intravenous drug administration for 4 days or longer provides better results and less toxicity that do bolus or short-duration infusions (id.). An example is provided of 5-fluorouracil which can be administered via arterial infusions for 14 days, followed by a similar rest period. As such, the claimed treatment cycle of administering the compound daily for 7, 14, 21, or 28 days, followed by 7 or 14 days without administration of the compound as recited in claim 31 would have been prima facie obvious. Pages 1065 to 1072 of Cecil discuss administration of regimens for numerous antineoplastic agents. For example, Table 198-9 at page 1071 teaches administration of drugs in the range of 20-100 mg/day, 40 mg/day for 4-day pulses every 2-4 weeks, 5 mg tid (three times a day), 1-3 mg qd (every day), 20 mg qd (every day), 250 mg bid (twice a day), or 1 g IM biw (biweekly). Cytarabine is taught to be administered either by continuous infusion or in bolus doses by the intravenous or subcutaneous route for 5-7 days. Alternatively, cytarabine can be administered in doses of 1 to 3 grams every 12 hours for 3 to 5 days (page 1066, right column).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used preclinical pharmacokinetic testing in order to determine the optimal treatment regimen for administration of the claimed compound to human subjects for the

treatment of cancer as suggested and motivated by the combined teachings of the cited prior art. It is clear from the cited prior art that there are numerous possible administration regimens for the administration of anticancer agents. However, one skilled in the art would have been imbued with at least a reasonable expectation of success that by using known, routine methods of measuring pharmacokinetic parameters, an optimal dosing regimen for administration of the claimed compound would be attained.

In light of the teachings of Renhowe *et al.*, one skilled in the art would have been motivated to select 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one and use this compound for the treatment of cancers expressing VEGF (such as breast cancer as evidenced by Foekens *et al.*). In developing said compound for use in the treatment of human subjects having cancer, the skilled artisan would use the FDA guidelines to determine the format and content of the human pharmacokinetic and bioavailability section of a New Drug Application, which teaches that biopharmaceutic studies are required by the Food, Drug, and Cosmetic Act (page 1). Such studies include pharmacokinetic studies assessing the time course of drug and major metabolite concentrations in blood and other body compartments (pages 3-4). The studies provided in support of a New Drug Application, the most critical information is that showing (by measurement of plasma drug levels) the rate of drug absorption and delivery to the systemic circulation, and the rate of elimination by metabolic or excretory processes (page 4). Pharmacokinetic parameters should include C_{max}, AUC, t_{max}, K_{el}, V_d, etc. derived from each *in vivo* study (page 6).

Following these guidelines, the skilled artisan would have been led to: (1) administer the claimed compound to subjects using different known doses, routes, and administration regimens (such as those taught in Cecil); (2) measure the pharmacokinetic parameters of the drug following such administration; and (3) select the most efficacious and tolerable dose, administration route, and administration regimen combination. Such testing is routine in the art of the development of anticancer drugs as evidenced by Renhowe *et al.*, the FDA guidelines, and Cecil.

In light of the above discussion, the claimed treatment cycles are not seen as a patentable distinction over the cited prior art, which teaches, suggests, and motivates one skilled in the art to administer anticancer agents in different doses, via different administration routes, and using

different administration cycles in order to elicit the optimal therapeutic response with minimal toxicity.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, 9-15, 16-38, 49-51, 53-58, and 67-71 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 30 of U.S. Patent No. 6,605,617. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treating a patient in need of an inhibitor of vascular endothelial growth factor receptor tyrosine kinase comprising administering an effective amount of a formulation comprising a compound of any of claims 1, 8, 15, or 22 as recited in claim 30 of the '617 patent encompasses the treatment of the claimed cancers using any amount of the instantly claimed compound that is "effective". As such, Applicant's characterization of the Cmax and AUC values of the instantly claimed compound is not seen as a patentable distinction over the method claimed in the '617 patent. Further, the specification of the '617 patent, when used as a dictionary to define the claimed "effective amount" states that specific

dosages may be adjusted depending on conditions of the disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs (col. 60, lines 33-37). Any of the dosage forms containing effective amounts are taught to be "well within the bounds of routine experimentation and therefore, well within the scope of the instant invention" (col. 60, lines 38-40).

Applicant's arguments have been carefully considered but they are not deemed to be persuasive. Applicants argue that nothing in Renhowe et al. teaches or suggests that the compounds recited in claim 30 of the '617 patent are capable of inhibiting PDGFR, c-Kit, or FLT-3 kinases or that such compounds would be capable of treating cancers expressing such kinases. However, Applicants have presented no evidence that the treatment of a patient having cancer wherein the cancer expresses PDGFR, c-Kit, or FLT-3, would not also encompass the treatment of a patient in need of an inhibitor of vascular endothelial growth factor receptor tyrosine kinase, who Renhowe et al. teach are patients having cancer. In other words, Applicants have not provided any evidence that there are cancers that express PDGFR, c-Kit, or FLT-3 that do not also express VEGF.

Applicants further argue that claim 30 of the '617 patent fails to provide any guidance directing the skilled artisan to any particular compounds in the recited genus. However, the Examiner notes that the claimed compound is exemplified as a compound of the claimed genus useful in the treatment methods disclosed therein (Example 109 at column 86, lines 64-66 and column 97, lines 23-24). The Examiner respectfully submits that one skilled in the art would have been motivated to use the '617 patent specification as a Dictionary to define what compounds of the recited genus are exemplified as more useful and active compounds of the invention. As such, the '617 patent provides sufficient guidance to select the claimed compound for use in the method of treatment recited in claim 30.

Claims 1-38, 49-51, 53-58, 67, and 69-71 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 7,470,709 in view of **Berge *et al.*** (J. Pharm. Sci., 1977, vol. 66, no. 1, pages 1-19). Although the conflicting claims are not identical, they are not patentably distinct from each other because the methods of treating cancer in a patient comprising administering an effective amount of a

formulation comprising a compound of the formula recited in claim 1 of the '709 patent encompasses the treatment of the claimed cancers. For example, instant claims 67 and 69-71 recite the treatment of cancer selected from the group consisting of prostate, colorectal, breast, acute myelogenous leukemia, and myeloma. Claims 67 and 69-71 depend from instant claims 1, 36, 49, and 53, respectively and are thus cancers comprising cells expressing PDGFR, c-Kit, or FLT-3 as recited in the instant claims. The claims of the '709 patent explicitly recite the treatment of acute myelogenous leukemia, breast carcinoma, colon cancer, and prostate cancer, including treatment of these cancers with compounds encompassing the compound recited in the instant claims. For example, the compound recited in claims 11, 14-15, and 17 of the '709 patent differs only in the ring position of the substituted piperazine group. It would have been *prima facie* obvious to "ring-walk" the piperazine group in the compound recited in claims 11, 14-15, and 17 of the '709 to arrive at the claimed compound. The skilled artisan would have been imbued with at least a reasonable expectation that this compound would also be effective in the treatment of cancers recited in the '709 patent claims.

With regard to the claimed C_{max}, ng/mL, and AUC values, the claims of the '709 patent recite administration of "an effective amount" of the claimed compounds. As such, in the absence of evidence to the contrary, an "effective amount" as recited in the '709 patent claims will necessarily result in the claimed C_{max}, ng/mL, and AUC values. Accordingly, recitation of Cmax, ng/mL, and AUC ranges in the instant claims is not seen as a patentable distinction over the treatment methods disclosed and claimed in the '709 patent.

With regard to claims 7 and 14, claim 1 of the '709 patent recites administration of a compound or a pharmaceutically acceptable salt of the compound. While the '709 patent does not disclose the claimed lactate salt, Berge et al. teach that the chemical, biological, physical, and economic characteristics of medicinal agents can be manipulated and, hence, often optimized by conversion to a salt form (page 1, left column). In this regard, Berge *et al.* teach a list of FDA approved commercially marketed salts, including the instantly claimed lactate salt (Table 1). Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to formulate 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one as suggested and motivated in the '709 patent as a lactate salt and use this salt to treat the cancers recited in the '709 patent claims.

With regard to claims 16-19 and 21-22, the specification of the '709 patent is used as Dictionary to define the intended means of "administering" as recited in the '709 patent claims. In this regard, the compounds disclosed in the '709 patent may be formulated in pharmaceutical compositions comprising pharmaceutically acceptable carriers, excipients, binders, diluents, and the like as well as thickeners, buffers, sweeteners, and flavoring agents (col. 140, line 38 to col. 142, line 21).

With regard to claim 23, the compounds of the invention may be formulated in compositions for various routes of administration, such as in injectable dosage forms (col. 140, line 53 to col. 142, line 13).

With regard to claims 24-27, 31-35, and 50-51, specific dosages of the compounds of the invention may be adjusted depending on conditions of the disease, the age, body weight, general health conditions, sex, and diet of the subject, dose intervals, administration routes, excretion rate, and combinations of drugs (col. 142, lines 36-42). Any of the dosage forms containing effective amounts are taught to be "well within the bounds of routine experimentation and therefore, well within the scope of the instant invention" (col. 142, lines 39-42). As such, optimization of the dosing regimen for "administering" the compounds recited in the '709 patent claims would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made. Because the '709 patent claims fully encompass any "administering" any doses via any administration route using any dosing regimen, the claimed administration regimens are not patentably distinct from the administering methods recited in the '709 patent claims.

At most, Applicants have engaged in verification testing to optimize the dose, administration route, and dosing regimen of the clearly suggested "administering" methods disclosed and claimed in the '709 patent. Such optimization is universal and even common-sensical when one skilled in the art considers that determining optimal dose, administration route, and administration regimens is required for clinical testing of a therapeutic agent.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614